

MATERIAL SAFETY DATA SHEET

Boehringer Ingelheim Pharmaceuticals, Inc.

**Alupent® Inhalation
Aerosol**

900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
(203) 798-5521 9AM - 4PM EST

DATE REVISED 04/13/07

EMERGENCY TELEPHONE NUMBER
CHEMTREC - 24 hours
1-800-424-9300

1. SUBSTANCE IDENTIFICATION

CHEMICAL NAME: 1-(3,5-dihydroxyphenyl)-2-isopropylaminoethanol sulfate
CAS TYPE: 1

GENERIC NAME: Metaproterenol Sulfate

MOLECULAR FORMULA: $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$

TRADEMARK: **Alupent® Inhalation Aerosol**

MOLECULAR WEIGHT: 520.59

PRODUCT USE: Bronchodilator³

CAS NUMBER²: 5874-97-5

SYNONYMS: Alotec, Metraprel, Orciprenaline Sulfate, Novasmasol, TH-152

2. COMPONENTS PER UNIT DOSE

MATERIAL

Active Ingredient:

Metaproterenol Sulfate

Excipients:

Sorbitan Trioleate

Dichlorodifluoromethane

Dichlorotetrafluoroethane

Trichloromonofluoromethane

EXPOSURE LIMITS

15 $\mu\text{g}/\text{m}^3$ BIEL*

No TLV established*

1000 ppm TWA*

1000 ppm TWA*

1000 ppm Ceiling*

* As per 2005 ACGIH

*BIEL is the BI Exposure Control Level. Where lower governmentally imposed occupational exposure limits exist, such limits should take precedence.

3. HAZARD IDENTIFICATION

EMERGENCY OVERVIEW

Pressurized containers may explode when heated.

Will not burn. If involved in a fire, material emits toxic fumes. Use extinguishing media suitable for the material that is burning.

CONTRAINDICATIONS: This product should not be used by patients with a history of cardiac arrhythmias (irregular heart rhythm) associated with tachycardia (rapid heart beat).

Although rare, this product can cause immediate hypersensitivity in patients. Therefore, **Alupent® Inhalation Aerosol** should not be used by patients who have had a previous allergic reaction to any of the product's components.

ADVERSE REACTIONS TO PRODUCT: Difficulty in breathing, nervousness, headache, dizziness, palpitations, gastrointestinal distress, tremor, throat irritation, nausea, vomiting, cough, and worsening of asthmatic symptoms.

ROUTES OF ENTRY: Inhalation, Ingestion, Skin and Eye contact.

ACUTE EXPOSURE: Eye, skin and/or respiratory irritation.

SIGNS AND SYMPTOMS OF EXPOSURE: Possible allergic reaction to dust if inhaled (breathed), ingested (swallowed), or in contact with skin, tachycardia (rapid heart beat), hyper/hypotension (high/low blood pressure), palpitations, nervousness, tremor, nausea, vomiting, dizziness, fatigue, malaise (feeling sick), insomnia, angina (severe chest/throat pain), arrhythmias (irregular heart rhythm), and worsening of asthmatic symptoms.

CHRONIC EXPOSURE: Possible hypersensitization (development of abnormal sensitivity).

MEDICAL CONDITIONS POTENTIALLY AGGRAVATED BY EXPOSURE: Dust allergies, pre-existing respiratory conditions, heart and circulatory conditions, hypertension (high blood pressure), hyperthyroidism, diabetes, convulsive disorders.

CARCINOGENICITY: Not listed as carcinogen/potential carcinogen by NTP, IARC Monographs or OSHA.

4. EMERGENCY FIRST AID PROCEDURES

Persons developing anaphylactic (life-threatening) reactions, such as difficulty in breathing or unconsciousness, must receive immediate medical attention.

INGESTION: Rinse mouth out with large amounts of water. Do not induce vomiting or give anything by mouth to an unconscious or convulsing person. Seek medical attention.

INHALATION: Remove affected person to a well ventilated area and get immediate medical attention. If breathing becomes difficult, give oxygen. If breathing stops, start artificial respiration.

SKIN CONTACT: Remove contaminated clothing. Flush affected area with copious amounts of water. If irritation or rash develops, get medical attention.

EYE CONTACT: Flush eyes with large amounts of running water for 15 minutes. Get immediate medical attention.

NOTE TO PHYSICIAN: Treat symptomatically.

5. FIRE AND EXPLOSION HAZARD DATA

Flash Point	Flammable Limits	
	Upper	Lower
N/A	N/A	N/A

FIRE EXTINGUISHING MEDIA: Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.

SPECIAL FIRE FIGHTING PROCEDURES: As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing. Use water spray to keep fire-exposed containers cool and protect against all exposures.

UNUSUAL FIRE AND EXPLOSION HAZARDS: Pressurized containers may explode when heated. When heated to decomposition, material emits toxic fumes of nitrogen, carbon, sulfur, acid gases and phosgene.

6. SPILL AND ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN THE EVENT OF A SPILL: Wear approved respirator and chemically compatible gloves if containers have been compromised. Vacuum or sweep up spillage. Avoid creating dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area, wash down spill site, and control wash water.

7. PRECAUTIONS FOR SAFE HANDLING AND USE

HANDLING AND STORAGE PRECAUTIONS:

WARNING - CONTENTS UNDER PRESSURE

Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120° F. KEEP OUT OF REACH OF CHILDREN

Avoid contact with eyes, skin or clothing. Avoid breathing aerosol. Store in airtight container. Protect from light and extreme heat.

OTHER PRECAUTIONS: Wash thoroughly after handling material. Wear fresh clothing daily. Wash contaminated clothing before reuse.

8. CONTROL MEASURES³

ENGINEERING CONTROLS: Not generally required when handling containers. (See section 2 for exposure limits.)

RESPIRATORY PROTECTION: The need for respiratory protection should be determined by an industrial hygiene survey. (See Section 2 for exposure limits.) NIOSH/MSHA approved respirators for protection should be used if respirators are found to be necessary.

VENTILATION: General ventilation should be adequate to maintain exposure levels below recommended established exposure limits. If general ventilation is not sufficient, local exhaust is recommended.

PERSONAL PROTECTIVE EQUIPMENT: Not generally required when handling final product. If containers are compromised or exposure to the active ingredient or mixture is likely wear:

Eye Protection: Safety glasses w/ sideshields or goggles	Hand Protection: Neoprene gloves
Protective Clothing: Laboratory coats	Other: Eye wash

WORK/HYGIENIC PRACTICES: Do not permit eating, drinking or smoking near this material.

9. PHYSICAL/CHEMICAL CHARACTERISTICS

APPEARANCE AND ODOR: White micronized powder in inert propellants, with little or no odor.

Boiling Point: N/A	Specific Gravity: N/A
Vapor Pressure (mmHg): N/A	Melting Point: 396-397° F (202-203° C)
Vapor Density: N/A	Evaporation Rate: N/A
Water Solubility: Soluble	pH: N/A

10. REACTIVITY DATA

STABILITY: Stable.

CONDITIONS TO AVOID: None known.

INCOMPATIBLE MATERIALS: Alkalis, heavy metal ions, and oxidizing agents.

HAZARDOUS DECOMPOSITION OR BY-PRODUCTS: When heated to decomposition, material emits toxic fumes of nitrogen, carbon, sulfur, acid gases and phosgene.

HAZARDOUS POLYMERIZATION: Will not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY: (Active Ingredient)

- 5538 mg/kg oral - rat LD₅₀
- 4800 mg/kg oral - mouse LD₅₀
- 455 mg/kg inhalation - dog LD₅₀
- 750 mg/kg inhalation - monkey LD₅₀

TERATOGENICITY: - PREGNANCY CATEGORY C: **Risk to human fetuses cannot be ruled out.** Human studies are lacking, however, animal studies are positive for fetal damage. Consult physician before using if you suspect you are pregnant or nursing.

Teratogenic and embryotoxic in rabbits when given at 620 times the human inhalation dose and at 100 mg/kg or 62 times maximum recommended human oral dose. These effects include skeletal abnormalities (bone deformities), hydrocephalus (fluid on the brain), and skull bone separation.

Recent studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

CARCINOGENESIS/MUTAGENESIS/IMPAIRMENT OF FERTILITY: In an 18-month study in mice, Alupent produced a significant increase in benign ovarian tumors in females at doses corresponding to 31 and 62 times the maximum recommended dose (based on a 50kg, individual). The relevance of these findings to man are unknown. Mutagenic studies with Alupent have not been conducted.

ACUTE TOXICITY for Excipients:

Freon F-11 Animal Toxicity Data:

1. LD50 Guinea pig inhalation 250,000 ppm/30 min
2. LD50 Rat inhalation 100,000 ppm/30 min
3. LD50 Rat oral 3725 mg/kg
4. LC50 Mouse inhalant 10,000 ppm/ 30 minutes

Freon F-11 Human Toxicity Data

1. By inhalation, large, acute doses have resulted in cardiac sensitization (arrhythmia) or bronchial constriction leading to death.
2. Human exposure to 1000 ppm, 8 hr/day, 5 days/wk for a total of 18 exposures had no untoward subjective effects, & there were no changes in the electrocardiogram or pulmonary function tests. The venous blood levels of F11 after 8 hr were as high as 4.69 ug/ml. The gradual attainment of this level represents a low uptake of the gas.
3. Bradycardia is the usual response in human subjects inhaling 10% of CFC 11. It is reasonable to suggest that bradycardia in man originates from irritation of the upper respiratory tract, & that cardiac effects can be initiated prior to absorption of CFC 11 in the lungs.
4. Gas of low toxicity but not entirely inert.
5. May be central nervous system depressant in high concentration.

Freon F-12 Non-Human Toxicity Values:

1. LD50 Mouse inhalation 760,000 ppm/30 min
2. LD50 Guinea pig inhalation >800,000 ppm/30 min
3. LD50 Rabbit inhalation >800,000 ppm/30 min
4. LD50 Rat single oral >1 g/kg
5. LD50 Rat inhalation >800,000 ppm/30 min

Freon F-12 Human Toxicity Data

1. Fatal case of bronchopneumonia /reported/ in man who punctured freezing coil of refrigerator containing F-12. It is probable that he aspirated cold concentrated vapor or liq, or was exposed to degradation products of refrigerant compound.
2. If inhaled at 5% by vol concentration induces dizziness in man. If inhaled at 15% concentration, loss of consciousness results.
3. Studies on volunteers showed that inhalation of 10,000 ppm of fF12 for 2.5 hr causes 7% reduction in standardized psychomotor scores.
4. At concentration of 1000 ppm for 8 hr/day, 5 days/wk for total of 17 repetitive exposures, there were no untoward subjective responses & no abnormal physiological responses of lungs or heart.
5. Concentration as high as 27,000 ppm of F12 for 15 to 60 sec caused increase in airway resistance & electrocardiographic changes

Freon F-114 Non-Human Toxicity Values:

1. CFC-114 caused no effects in mice, rats, guinea-pigs, cats, or dogs after intermittent exposure to concentrations as high as 711 g/cu m (100 000 ppm). At higher dose levels (995-1422 g/cu m; 140,000-200,000 ppm) signs of intoxication were noted in guinea-pigs, dogs, rats, and mice.
2. Exposure at 20% by volume caused tremors and convulsions in dogs. after single 8-hour exposures the animals recovered, but repeated exposures for 8 hours daily were fatal after 3 or 4 days. single 16-hour exposures were also lethal to dogs.
3. Dogs survived 21 eight-hr exposures at 142,000 - 150,000 ppm CFC-114; the animals showed slight blood changes & symptoms ranging from in coordination to occasional convulsions.
4. Dogs survived eight-hr exposures at 200,000 ppm CFC-114; however a single 16-hr exposure or three to four 8-hr exposures were lethal. High concentration produced clinical signs of tremors, convulsions, & incoordination.
5. Concentrations around 1% caused slight irritation in guinea pigs; concentrations of 2 to 4.7% caused distinct irritation and increased respiration, but no pathological changes after 2 hours.
6. An increase in red blood cells, hemoglobin, & /immature/ forms of polymorphonuclear leucocytes were reported in dogs following exposure to vapors

F 114 Human Toxicity Data

1. In one study, ten subjects were exposed to CFC-11, CFC-12, and CFC-114; two mixtures of CFC-11 and CFC-12; & a mixture of CFC-12 and CFC-114)breathing concentration between 16 & 150 g/cu m [2300 & 21,400 ppm]) for 15, 45, or 60 sec. Significant acute reduction of ventilatory lung capacity was reported in each case, as well as bradycardia & increased variability in heart rate & atrioventricular block. It was concluded that the mixtures exerted stronger respiratory effects than individual chlorofluorocarbons at the same level of exposure.

12. ECOLOGICAL INFORMATION

WARNING: Contains trichloromonofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), substances which harm public health and the environment by destroying ozone in the upper atmosphere.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL CONSIDERATIONS: Dispose of in accordance with local, state and federal regulations. Recommended method is incineration at a facility capable of handling pressurized canisters.

14. TRANSPORT INFORMATION

D.O.T. Proper Shipping Name: Exempt for all DOT rules
Hazard Class: N/A
Identification Number: N/A
Packing Group: N/A
Label: N/A
Emergency Response Guidebook - N/D

15. REGULATORY INFORMATION

This product contains trichloromonofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), which have been designated as Class I, Ozone Depleting Substances, in 40 CFR 82, Subpart A, Appendix A.

Medical aerosols are excluded from the definition of a "controlled product" under 40 CFR Part 82 - Protection of Stratospheric Ozone.

16. OTHER INFORMATION

ABBREVIATIONS:

BIPI - Boehringer Ingelheim Pharmaceuticals, Inc.

N/A - Not applicable.

PREPARATION INFORMATION

Prepared by: Environmental Affairs & Safety.

Date Revised: 04/13/07

Replaces: 3/25/03

REVISION INFORMATION: Section 14: Transport Information, Section 2 Components Per Unit Dose-
updated exposure limits

The opinions expressed herein are those of qualified experts within Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). We believe that the information contained within this MSDS is current as of the date issued. Since the use of this information and these opinions and the conditions of use of this material are not within the control of BIPI, it is the user's obligation to determine the conditions of safe use of this material. BIPI urges the users of this product to study this MSDS and become aware of any hazards associated with this material. In the interests of safety, the information contained in this MSDS should be made available to your employees, agents and contractors who handle this material.

SEE CURRENT PACKAGE INSERT FOR FURTHER INFORMATION

REFERENCES

1. NIOSH – RTECS® *Registry of Toxic Effects of Chemical Substances*, 1993-2003
2. BIPI – Material Safety Data Sheet for Alupent®, 4/98
3. Investigator's Brochure for Alupent®.
4. Physician's Desk Reference®, 1974-2003
5. REPROTOX® Reproductive Toxicology Center, 8/1/02
6. DRUGDEX® Drug Evaluations, 1974-2003